IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTOR :	Douglas H. ROBINSON
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FILING DATE:	January 16, 2001
TITLE:	METHODS FOR ISOLATION OF BACTERIA CONTAINING EUKARYOTIC GENES
ART UNIT:	1645
EXAMINER:	Robert A. ZEMAN

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APPEAL BRIEF

SIR:

This is a brief in support of an appeal filed in the above-identified application.

I. REAL PARTY IN INTEREST

The real party in interest is the applicant, Douglas H. Robinson.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to Appellant, Appellant's legal representative, or Assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in this Appeal.

III. STATUS OF CLAIMS

Original claims 1-3, 15-18, 24 and 25, and new claims 26-29, have been canceled. Claims 4-14, 19-23 and 30-31 are pending, have all been finally rejected, and all are on appeal.

IV. STATUS OF AMENDMENTS

No amendments were filed subsequent to final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The independent claims presented on appeal are claim 30 and claim 31. The present invention as recited in claim 30 relates to methods comprising the following steps:

> (a) preparing a culture of virally-infected eukaryotic cells that is free of any overt microbiological contamination, in a sterile eukaryotic cell culture medium,
>
> (b) subjecting the culture of step (a) to an anaerobic culturing phase under sterile conditions wherein the culture is subjected to anaerobic culturing conditions corresponding to an atmosphere of 0-2 v/v % oxygen, for a period of time between about 18 and 24 hours, followed by
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> (c) exposing the culture of step (b) under sterile conditions to oxygen conditions corresponding to an atmosphere containing greater than 2 v/v % oxygen, followed by
>
> (d) subjecting the culture of step (c) to a second anaerobic culturing phase under sterile conditions wherein the culture is subjected to anaerobic culturing conditions corresponding to an atmosphere of 0-2 v/v % oxygen, for a period of time of between about 18 and 24 hours, followed by
>
> (e) subjecting the culture of step (d) to a second aerobic culturing phase under sterile culturing conditions and corresponding to an atmosphere containing greater than about 2 v/v % oxygen in a sterile bacterial cell culture medium, and

(f) identifying in the culture of step (e) a cell that is identifiable as a bacteria, and contains a eukaryotic and/or viral gene.

Support for claim 30 can be found in the specification at, for example, page 5, line 29 to page 6, line 2, page 6, lines 24-30, page 9, lines 5-14 and lines 26-29, page 10, lines 25-26, and each of the examples (page 18, line 4 to page 34, line 24).

The present invention, as recited in claim 31, also relates to pleiomorphic cells characterized by being non-transgenic, derived by a process comprising steps corresponding essentially to steps (a) to (f) of claim 30, and containing at least one gene evolved from the genome of the eukaryotic cell from which it is derived. Support for claim 31 can be found in the specification at, for example, page 5, line 29 to page 6, line 2, page 6, lines 24-30, page 9, lines 5-14 and lines 26-29, page 10, lines 25-26, and each of the examples (page 18, line 4 to page 34, line 24). Further support can be found at page 7, lines 2-25, page 29, lines 10-22.

The unusual feature of the claimed invention is that by utilizing the methods thereof, it is possible to obtain, from a culture of virally-infected eukaryotic cells free of any overt microbiological contamination, cells that can be identified as bacteria based on such characteristics as morphology, ultrastructure and Gram-staining, which contain a eukaryotic and/or viral gene, without the introduction of the gene(s) into the cell by traditional molecular biological techniques during the process. By the exercise of scrupulous attention to sterility, and the use of multiple controls in the methods, it has been confirmed that the cells produced are not the product of contamination at any point in the process, and so are not merely the result of contaminating bacteria overgrowing the starting eukaryotic cell culture.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. 35 USC § 101, Lack of Utility

Claims 4-14, 19-23 and 30-31 stand rejected under 35 USC § 101, as being inoperative and therefore lacking utility.

B. 35 USC § 112, First Paragraph, Lack of Enablement

Claims 4-14, 19-23 and 30-31 stand rejected under 35 USC § 112, first paragraph, as being based on a specification that does not enable a person skilled in the

art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

C. 35 USC § 112, First Paragraph, Lack of Written Description

Claims 4-14, 19-23 and 30-31 stand rejected under 35 USC § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

D. 35 USC § 112, Second Paragraph

Claims 4-14, 19-23 and 30-31 stand rejected under 35 USC § 112, second paragraph, as failing to set forth the subject matter which applicant regards as his invention.

Claims 4-14, 19-23 and 30-31 stand rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention.

Claim 31 stands rejected under 35 U.S.C. § 112, second paragraph, as being vague and indefinite in the use of the phrase "gene evolved from the genome of said eukaryotic cell."

VII. ARGUMENT

A. Background

This case has been pending for over ten years, and this is the second time that it has been before the Board. On the first appeal, Appeal No. 2004-2077, the Board found that the absence of a terminal disclaimer on file, coupled with the Examiner's failure to list his obviousness-type double-patenting rejection in his Answer as pending, rendered the status of the case unclear, as the issue of double patenting (in the absence of a terminal disclaimer, if the rejection was still pending) could potentially dispose of the case. The Board, therefore, did not issue a ruling on the merits of the pending rejections, and remanded the case for clarification of the double-patenting issue. January 31, 2205 Remand to the Examiner ("Remand"), page 4.

However, the Board did provide its observations regarding the claims and the invention, and on the pending rejections and the Applicant's arguments *contra*, and their relative strengths and deficiencies, "in an effort to advance prosecution." Remand, page 6. The Board noted that the Applicant's position rested in part on aspects of the invention that were not reflected in the claim language. Remand, page 7. The Board also noted that there did not appear to be any evidence in the record to support a number of the Examiner's arguments. Remand, page 9. The Board also encouraged both the Applicant and the Examiner "to take a step back, and reconsider the administrative record to determine if the arguments of record are supported by an adequate evidentiary basis on this record." Remand, page 10. The Board, in particular, "remind[ed] the examiner that findings of fact and conclusion of law by the USPTO must be made in accordance with the Administrative Procedure Act, 5 U.S.C. § 706(A), (E), 1994," as "our reviewing court has held that findings of fact must be supported by substantial evidence within the record." Remand, pages 9-10 (citations omitted).

The Examiner issued a non-final Office Action on October 12, 2005, rejecting all pending claims for the same reasons on which the previously-appealed rejection was based. The Applicant filed an Amendment and Request for Reconsideration on February 10, 2006, canceling the independent claims and substituting new claims therefor, canceling or amending certain dependent claims, all of which the Applicant believed brought the claims in line with the observations made by the Board on remand, and placed them in form for allowance. The Applicant requested an interview with the Examiner, and his Supervisor (SPE Lynette Smith), which took place on May 3, 2006. No progress whatsoever was made during the interview, the Examiner simply stating, without elaboration, that the Applicant's amendments did not overcome his rejections. The Applicant was advised by SPE Smith that the case would be forwarded to Quality Assurance for review prior to the next Office Action. The Examiner subsequently issued a final Office Action on June 6, 2006, rejecting all of the pending claims for the same reasons stated in the previous rejection. A timely Notice of Appeal was filed on September 6, 2006.

B. The Rejection Under 35 USC § 101 Lacks Merit, and Furthermore Has Been Previously Rejected By The Board As Lacking Merit

The Examiner has maintained his rejection of the claims under 35 USC § 101, stating that "[t]he claimed invention is not supported by either a credible utility or a well

established utility, as the **disclosed invention is inoperative**." Office Action, page 4 (emphasis original). The Examiner has cited no evidence in the record in support of this rejection, other than dictionary definitions of terms that do not even appear in the claims (Office Action, page 4), nor does he introduce any new evidence into the record.

1. The Examiner has not applied the rejection to the claims as presently pending

As an initial matter, the Examiner states that this rejection is maintained "for reasons set forth in the previous Office action in the rejection of claims 1-29" (Office Action, page 4), however he does not point out how this rejection applies to the claims *as presently pending*. Not only have the previously-pending claims been amended, but the original independent claims have been canceled and replaced with new claims. The Examiner nowhere establishes, or even explains, with specificity how this rejection applies to the new claims, a fact evident from his continued reference to the claimed invention as "a method for **producing a bacterium**," when this language no longer appears in the pending claims. *C.f.*, Office Action, page 4 (emphasis original). The pending claim 30 claim does not recite "production" of a "bacteria," as the Examiner continues to characterize the claims. Furthermore, claim 31 recites a *composition of matter*, a fact that is not even mentioned in the Examiner's rejection under § 101. For this reason alone this rejection should be reversed, as it is not directed to the claims as presently pending. *C.f.*, MPEP § 2107.02 (Rev. 5), page 2100-28 ("The claimed invention is the focus of the assessment of whether an applicant has satisfied the utility requirement"); *Phillips v. AHW Corp.*, 415 F.3d 1303, 1312, 75 USPQ2d 1321, 1325 (Fed. Cir. 2005) (*en banc*) ("It is a bedrock principle of patent law that the claims define the invention to which the patentee is entitled the right to exclude.") (internal quotations omitted); *In re Hiniker Co.*, 150 F.3d 1362, 1369, 47 USPQ2d 1523, 1529 (Fed. Cir. 1998) ("the name of the game is the claim").

2. If applicable to the pending claims, the rejection is without merit

Assuming that this § 101 rejection does apply to the claims as presently pending, it is without merit.

a. The rejection of composition of matter claim 31 is improper

The Examiner asserts only that the claimed *methods* are inoperable, and therefore lack utility. *See, e.g.,* Office Action, page 4 ("The claims are drawn to a method for **producing a bacterium**") (emphasis original); page 5 ("Therefore, the specification fails to show a clear correlation between culturing retrovirally infected animal cess in the amount of oxygen given and the 'creation' (i.e., the production) of a new species of bacteria"); page 6 ("As Applicant has failed to demonstrate that the execution of the claimed method steps would result in the **production of a bacterium containing a eukaryotic and/or viral gene**, the rejection is maintained") (emphasis original). The Examiner does not dispute any of the several statements in the specification regarding the utility of the *cells* produced by the claimed methods. *See,* Specification, pages 5-6; page 13, line 31 to page 17, line 29. Claim 31 is a *composition of matter* claim, directed to the cells. There is, therefore, no basis provided by the Examiner upon which a rejection of claim 31 under § 101, for lack of utility, could stand. The rejection is, therefore, improper as applied to claim 31, and for at least this reason should be reversed as to that claim.

b. The rejection of the method claims is without merit

The Examiner also does not dispute that the processes recited in claim 30 and its dependent claims do, in fact, operate to provide the cells described in step (f) of claim 30. Rather, the Examiner takes issue with the *underlying mechanism* by which he assumes the claimed methods *achieve* the claimed results. The Examiner asserts that "Applicant is calling for the *de novo* 'creation' of a new species and/or the 'creation of a life form,' i.e., the bacterium, from eukaryotes without the introduction of bacterial genes or the bacteria themselves." Office Action, pages 4-5. This, the Examiner states, is contrary to "the best of scientific knowledge," noting that "Louis Pasteur effectively disproved the principles of spontaneous generation at the end of the last century in historical experiments." Office Action, page 5. The Examiner concludes that "the specification fails to show a clear correlation between culturing retrovirally infected animal cells in the amount of oxygen given and the 'creation' (i.e., the production) of a new species of bacteria." *Id.* Thus, the Examiner further concludes, "Applicant has failed to demonstrate that the execution of the claimed method steps would result in the

production of a bacterium containing a eukaryotic and/or viral gene, [so] the rejection is maintained." Office Action, page 6 (emphasis original).

The Examiner has equated "production" with "creation," neither of which is a term appearing in the claims, and concludes that because the Applicant has not demonstrated that execution of the claimed method produces/creates bacteria, the invention must be inoperative.[1] There are a number of flaws in this argument. First, the claims do not recite either "*de novo* creation of a species," or "creation of a life form," or "spontaneous generation" in the sense of the principle of the spontaneous generation of life from lifeless matter that was disproved by Dr. Pasteur. Nor do the claims recite "production" or "creation" of a bacteria. The claims recite a method comprised of a specific series of steps, which provide a certain, clearly defined, type of cell ("a cell that is identifiable as a bacteria, and contains a eukaryotic and/or viral gene"). *Phillips*, 415 F.3d at 1312, 75 USPQ2d at 1325 (*en banc*) ("It is a bedrock principle of patent law that the claims define the invention to which the patentee is entitled the right to exclude.") (internal quotations omitted); *c.f.*, MPEP § 2107.02 (Rev. 5), page 2100-28 ("The claim is the focus of the assessment of whether an applicant has satisfied the utility requirement").

Second, and very significantly, the specification contains working Examples and experimental data which demonstrate that the practice of the recited method steps does indeed provide cells that are "identifiable as bacteria, and contain a eukaryotic and/or viral gene." *See*, Specification, Example 1 (pages 18-19), Comparative Example D (pages 23-26), Examples 3, 4, 4/A, and 5 (pages 27-34). The operability of the claimed methods is therefore demonstrated by experimental evidence. The Examiner has not shown this evidence to be, or even asserted it to be, in any way inaccurate, defective, or irrelevant to the question of utility. It therefore stands unchallenged, and presumptively accurate and truthful. *See, e.g., In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297

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[1] In the previous appeal, the Applicant stated that the dispute in this case was a matter of "semantics," to which the Board responded that "[s]emantic arguments regarding the scope of the claimed invention should have been resolved during prosecution." Remand, page 7, footnote 1. However, it is indeed semantic arguments such as the Examiner's equating "production" with "creation of a new life form," and the singular unhelpfulness of the Examiner in resolving these issues with the Examiner (despite repeated attempts by the Applicant to suggest and/or elicit alternative claim language that would satisfactorily describe the invention without raising issues such as the Examiner's "spontaneous generation" argument), which have made appeal to the Board necessary.

(CCPA 1974) (statement of utility in a specification must be taken a sufficient to satisfy § 101, unless there is reason to question the objective truth of the statement); *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) (specification presumptively accurate).

Third, the Examiner does not even mention the experimental evidence of operability provided in the specification, and instead focuses his arguments on the underlying mechanism. The possible underlying mechanism by which the claimed result is achieved (which the Examiner assumes is spontaneous generation of life) is not recited in the claim, nor is a knowledge or understanding of it needed in order to practice the claimed methods. It therefore is immaterial to the patentability of the claims. *See*, *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983) ("it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests"); *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989) ("it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works"); *accord*, *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1469 (Fed. Cir. 1999) ("statements that a physiological phenomenon was observed are not inherently suspect simply because the underlying basis for the observation cannot be predicted or explained. Therefore, the Board erred in suggesting that Cortright was required to prove the cause of the resultant hair growth.").

Fourth, the Examiner's arguments are contrary to the observations provided by the Board on Remand, which the Board expressly stated were made "in an effort to advance prosecution." Remand, page 6. In his last Amendment, the Applicant pointed out the observation by the Board that appears to support the argument that the record evidence shows that the claimed process, when practiced under sterile conditions, starts with cells identifiable as belonging to or coming from one species (a eukaryotic cell), and "resulted in the 'production'" of cells that are identifiable as belonging to another (a bacterium), or stated differently "*de novo* speciation," and that "[w]ith regard to the term 'identifiable' we note that according to the Steuer Declaration (paragraph 4), notwithstanding rigorously sterile conditions, the claimed method results in the 'production' of bacteria identified as *B. licheniformis*." Remand, pages 8-9. The Examiner dismisses these observations as "merely a summary of the Applicant's arguments and the Declaration of Dr. Steuer," and not an indication that the Board

agreed with those arguments. Office Action, page 6. On the contrary, the Board summarized the *evidence* in the record, not merely the Applicant's arguments. The Board stated that it was "unable to identify any evidence upon which the examiner relies upon to support [the examiner's] assertion." Remand, page 9. Neither did the Board find "evidence on this record to explain why these 'strains of bacteria' would contaminate cells cultured under sterile conditions, and even if they did why these 'strains of bacteria' would contain a eukaryotic and/or viral gene as required by the appellant's claimed invention." *Id.*

Significantly, the Examiner attempts to minimize the Board's comments by saying that "the Board clearly states that the Applicant's arguments are directed to inventions other than that being claimed (see page 7 of the Board's Brief)." *Id.* While of course the Board itself knows best it's own intention in making the above-quoted observations on Remand, when taken in context they appear to the Applicant as an indication of the Board's belief that the evidence of record supports the operability of the claimed invention. Though the Examiner is correct that the Board pointed out that the Applicant's arguments in his previous appeal were "directed to inventions other than that being claimed," the claims as amended and currently pending correct this by reciting that the starting cell culture be "free of any overt microbiological contamination," and that sterile conditions be maintained throughout the process, which corrects precisely the shortcoming in the language of the then-pending claims to which the Board was referring. The Examiner simply side-steps this fact by stating that "said deficiency in claim language was addressed in the rejection" (Office Action, page 6), failing to address in his latest rejection the fact that the claims were subsequently amended to overcome this "deficiency in claim language."

The Examiner also dismisses the Board's observation that there was no evidence of record "to explain why these 'strains of bacteria' would contaminate cells cultured under sterile conditions, and even if they did why these 'strains of bacteria' would contain a eukaryotic and/or viral gene as required by the appellant's claimed invention" (Remand, page 9) with the statement that the "comment by the Board was with regard to the properties of the 'recovered bacteria,'" which "cannot be construed as the Board agreeing that the claimed method is operative." Office Action, page 6. The logic of this statement escapes the Applicant. If the Board was, in fact, observing that based on the evidence of record the "recovered bacteria" of the claimed method were

not due to contamination of a sterile starting cell culture, and that even if they were contaminants this does not account for the fact that the cells produced by the claimed method contain a eukaryotic and/or viral gene, the Applicant does not see how this is *not* an indication that the process is operative – if the claimed methods permit recovery of cells identifiable as bacteria, which contain a eukaryotic and/or viral gene, and which are not contaminants of the starting cell culture, they are operative.[2]

What the Examiner has said in his rejection is, in effect, "I don't believe that your method is actually working the way you say it is." Aside from the fact that the Applicant has nowhere asserted that his invention operates by the spontaneous generation, or creation, of bacteria, the Federal Circuit has held that "it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests." *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983). This is because "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989); *accord*, *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1469 (Fed. Cir. 1999) ("statements that a physiological phenomenon was observed are not inherently suspect simply because the underlying basis for the observation cannot be predicted or explained. Therefore, the Board erred in suggesting that Cortright was required to prove the cause of the resultant hair growth.").

Whether or not the inventor has correctly, accurately, or even credibly, set forth "the scientific principles on which the practical effectiveness of his invention rests," and/or whether or not the Examiner agrees with or believes any statement made by the Applicant regarding the underlying mechanism or principle by which the claimed method operates, and/or whether or not the Examiner believes that some other, incredible, process would have to be at work, is all irrelevant to the issue of utility. The present claims do not require that the method function according to any particular mechanism or scientific principle, and the presumptively accurate specification disclosure demonstrates

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[2] With regard generally to his treatment of the Board's observations on Remand, the Examiner is disingenuous in the extreme in saying that his interpretation of the Board's comments is supported by the fact that the Board did not make a decision on the operativeness of the invention. Office Action, page 6. The Board determined that the unresolved question of double patenting was possibly dispositive of the entire case, and so did not make a decision as to *any* issue in the case (hence the remand). *See* Remand, pages 4 and 6.

with experimental data that the claimed methods operate to achieve the claimed result. *See*, *In re Jolles*, 628 F.2d 1322, 1327-28, 206 USPQ 885, 890-91 (CCPA 1980) (evidence provided by the applicant showing that claimed analogs had the same pharmaceutical activity as known anticancer drugs sufficient to establish utility in satisfaction of § 101); *compare*, *Brooktree Corp. v. Advanced Micro Devices*, 977 F.2d 1555, 1557, 24 USPQ2d 1401, 1412 (Fed. Cir. 1992) ("[t]o violate § 101 the claimed device must be *totally incapable of achieving a useful result.*") (emphasis added); *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984) (The PTO may reject a claim under § 101 for lack of utility "when there is *a complete absence of data* supporting the statements which set forth the desired results of the claimed invention.") (emphasis added).

It is the burden of the PTO to come forward with *evidence* that calls into question the applicant's showing of the operability, and thus the utility, of the claimed invention. The Federal Circuit has stated in no uncertain terms that the Patent Office *must* present countervailing facts and reasoning sufficient to call into question the presumptively accurate specification. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436,1441 (Fed. Cir. 1995); *Cortright*, 165 F.3d at 1357, 49 USPQ2d at 1466 (Fed. Cir. 1999) (PTO cannot make a rejection under § 101 for inoperability unless it has reason to doubt the objective truth of the statements contained in the written description.") (citing *In re Brana*). Thus, "the PTO *must* do more than merely question operability – it must set forth *factual reasons* which lead one skilled in the art to question the objective truth of the statement of operability." *In re Gaubert*, 524 F.2d 1222, 1224, 187 USPQ 664, 666 (CCPA 1975) (emphasis added). In the present case, where the specification provides experimental evidence of the operability of the claimed invention, the PTO must provide evidence or sound reasoning sufficient to call into question the accuracy or validity of that evidence. Despite being specifically directed by the Board to support his arguments with "substantial evidence"[3] in the record (Remand, pages 9-10), the Examiner has not even attempted to do so. Instead, the Examiner merely asserts the impossibility of what he assumes is the underlying mechanism involved, without providing any evidence to

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[3] "Substantial evidence is defined as that which a reasonable person might accept as adequate to support a conclusion." *Faulkner v. Inglis*, 79 USPQ2d 1001, 1005 (Fed. Cir. 2006).

support his assertions. The Examiner, therefore, has failed to make a *prima facie* showing of inoperability of the claimed methods.

Because the Examiner has failed to make a *prima facie* case that the pending claims are inoperable, and further because the evidence of record shows that the claimed invention has a specific and substantial utility, this rejection under § 101 is improper and should be reversed.

C. The Rejections Under 35 USC § 112, First Paragraph, Lack of Enablement, Lack Merit and Should Be Reversed

1. The bases for the rejection

The Examiner has maintained his rejection of the claims as lacking an enabling disclosure in the specification, "for the reasons set forth in the previous Office action in the rejection of claims 1-29." Office Action, page 7. The Examiner asserts that the specification is enabling only for "a method for isolating a bacteria comprising aseptically culturing retrovirally transformed human capillary microvascular endothelial cells (ATCC 11655)" according to specific culture steps, the final step being "isolating a bacterium from the culture (either *Staphylococcus aureus* ATCC 55589, *Staphylococcus capitis* ATCC 55590, *Staphylococcus hemolyticus* ATCC 55592, *Staphylococcus epidermidis* ATTC [sic] 55591 or *Micrococcus luteus* ATCC 55588)," but does not "reasonably provide enablement for methods for **producing** a bacterium that contains a eukaryotic and/or viral gene comprising culturing virally-infected eukaryotic cells under low oxygen conditions." Office Action, page 7 (emphasis original).

The Examiner asserts that "while the terms 'production' and 'producing' have been eliminated from the claims, the claimed method steps are still drawn to a method of producing a bacteria by culturing eukaryotic cells under specified conditions." Office Action, page 9. The Examiner contends that "it does not appear that the claimed method would be suitable for the production of bacteria from any and **all virally infected eukaryotic cells**," and that "there is no reasonable expectation that any and all types of bacteria may be 'produced' or even isolated from any and all cell cultures by the procedure claimed." Office Action, page 11 (emphasis original). According to the Examiner, "[t]he present invention would also require undue experimentation to practice in view of the unpredictable completion of the culturing steps." Office Action, page 12.

None of these asserted bases for lack of enablement have merit.

2. The claims do not recite "production of bacteria"

The Examiner states in his rejection that even though the claims to not recite the terms "production" and "producing," nonetheless "the claimed method steps are still drawn to a method of producing a bacteria by culturing eukaryotic cells under specific conditions." Office Action, page 9. Not only has the Examiner again based a rejection on language that is not present in the pending claims (a fact that he actually acknowledges in this rejection), he imports terms and limitations into the claims from the specification, in effect re-writing the claim in a way that fits within his *a priori* conclusion of no enablement:

> Moreover, the specification consistently refers to said methods steps as being a method of "producing a bacteria" (see pages 1, 5, 7, 9, 10 etc. . . for example).

Office Action, page 9.

"It is a bedrock principle of patent law that the claims define the invention to which the patentee is entitled the right to exclude." *Phillips*, 415 F.3d at 1312, 75 USPQ2d at 1325 (*en banc*) (internal quotations omitted). Claim terms are generally given their ordinary and customary meaning in the art. 415 F.3d at 1313, 75 USPQ2d at ___. "If the claim language is clear on its face, then our consideration of the rest of the intrinsic evidence is restricted to determining if a deviation from the clear language of the claims is specified." *Interactive Gift Express, Inc. v. CompuServe Inc.*, 256 F.3d 1323, 1331, 59 USPQ2d 1401, 1407 (Fed. Cir. 2001). Though it is proper to turn to the specification for clarification when an ambiguity exists in a claim,

> [i]n order to overcome [the] heavy presumption in favor of the ordinary meaning of claim language, it is clear that 'a party wishing to use statements in the written description to confine or otherwise affect a patent's scope must, at the very least, point to a term or terms in the claim with which to draw in those statements.' [Quoting *Renishaw PLC v. Marposs SpA*, 158 F.3d 1243, 1248 (Fed. Cir. 1998).] That is, terms cannot be narrowed by reference to the written description or prosecution history unless the language of the claim invites reference to those sources. [Citation omitted] In other words, there must be a textual reference in the actual language of the claim with which to associate the proffered claim construction.

Johnson Worldwide Assocs. v. Zebco Corp., 175 F.3d 985, 989-990, 50 USPQ2d 1607, 1610 (Fed. Cir. 1999). No term in the present claims is in need of the re-definition advanced by the Examiner. He has not pointed to any term that is ambiguous and in need of definition by resort to the specification and prosecution history, nor has he identified any claim term that has been given in the specification a special definition by the inventor that is at variance with its ordinary and customary meaning in the art.

While claims are to be read in light of the specification (*Phillips*, 415 F.3d at 1315, 75 USPQ2d at 1327), it is improper, as a matter of law, to import a limitation into a claim from the specification. *Markman v. Westview Industries, Inc.*, 52 F.3d 967, 980, 34 USPQ2d 1321, 1330 (Fed. Cir. 1995); *Renishaw PLC v. Marposs SpA*, 158 F.3d 1243, 1248, 48 USPQ2d 1117, 1120 (Fed. Cir. 1998). By characterizing the claimed methods as methods of "producing a bacterium," the Examiner has ignored the clear and unambiguous meaning of the claim language, and substituted language from the specification that alters its meaning without providing any textual reference in the claims that invites such alteration, nor indeed identifying any term in need of definition. This improper re-definition of the claims colors the entire rejection (and indeed, the entire Office Action). Because it is based on an improper construction of the claims, this rejection is improper, and should be reversed.

3. The claims do not require isolation of "any and all bacteria" from "any and all" virally-infected eukaryotic cell lines

The Examiner asserts that the specification does not enable "production of bacteria from **any and all virally infected eukaryotic cells**" (Office Action, page 11). This not only overstates the scope of the claims (they do not require production of bacteria from "any and all virally infected eukaryotic cells), it also applies an incorrect standard for enablement. The Federal Circuit time and again has stated that § 112, first paragraph, does *not* require that the invention function in each and every embodiment encompassed by the claims. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984) ("Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid."). In fact, the Federal Circuit has expressly held that the enablement requirement is met if the specification enables *any mode* of making and using the invention. *Engel Industries v. Lockformer Co.*, 946 F.2d 1528, 1533, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991). So long as the specification, combined with the knowledge of a person of ordinary skill in

the art, permits one to practice the invention without undue experimentation, the enablement requirement is satisfied. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334, 65 USPQ2d 1385, 1400 (Fed. Cir. 2003) ("the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation.'"); *see also*, *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052,1071, 77 USPQ2d 1161, 1174 (Fed. Cir. 2005) ("Enablement does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise.").

In *Amgen*, the Federal Circuit held that a patent claiming genetically-modified vertebrate cells producing defined amounts of human erythropoietin (EPO), which disclosed at least one mode for producing such EPO, fully met the enablement requirement of § 112, first paragraph, as a person having ordinary skill in the art would have no difficulty in determining such process variables as whether a particular promoter would work in a particular cell line, whether a particular cell line would produce human EPO in culture, and whether a particular promoter could be operatively linked to control transcription of human EPO DNA, and because "the differences between using the two described mammalian (and vertebrate) cells and other such cells were very small and easily accommodated by the artisan." *Amgen*, 65 F.3d at 1336-37, 1338, 65 USPQ2d 1401-03. The Federal Circuit stated that "[w]ith these factual findings before us, [the defendant] cannot prevail *simply by reasserting in a conclusory manner* that Amgen's disclosure does not enable the transformation of all mammalian or vertebrate cells or the production of human EPO." 65 F.3d at 1337, 65 USPQ2d at 1402 (emphasis added).

The case of *Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 56 USPQ2d 1332 (Fed. Cir. 2000) is particularly applicable in the present case. In *Ajinomoto* the Federal Circuit held that a claim to a method of genetically modifying a bacterium via directed mutation to produce an amino acid was enabled, because all of the methodology needed to practice the invention was known in the art. The Federal Circuit approved of the lower court's finding that

> [d]espite the diversity existing among bacteria, practitioners of this art were prepared to carry out the identification, isolation, recombination and transformation steps required to practice the full scope of the claims.

Ajinomoto, 228 F.3d at 1345, 56 USPQ2d at 1337 (quoting District Court). The Examiner dismissed the *Ajinomoto* case with a single sentence: "*Ajinomoto v. Archer-Daniels-Midland Co.* is not germane as the instant case is drawn to a method of producing a bacterium from a eukaryotic cell and said method is not known in the art." Office Action, page 11. On the contrary, *Ajinomoto* is very germane to the present case, as the Examiner has, in part, based his rejection on the contention that

> the claimed method is unpredictable and would appear to depend on the type of cell cultured and the type of virus employed. It is unclear how the cell culture is chosen to have a reasonable a [sic] degree of certainty that bacteria as required can be "produced," in the absence of positive steps to modify existing bacteria and to assure the survival of the cell culture for a time period.

Office Action, page 12. *Ajinomoto* is germane because it finds enablement for an invention the practice of which requires, *inter alia*, selection of particular starting materials from a diverse universe of possible cell lines, and screening the resulting modified cells to determine whether or not the desired result had be achieved. Enablement was found because the basic technical knowledge needed to carry out the necessary process steps (once they were presented by the patentee) was within the ordinary skill in the art.

A very similar fact pattern exists in the present case: practice of the method steps of selecting starting materials, performing the recited culture steps, and characterization and identification of the cell produced thereby (thereby determining the success of the procedure), are all routine and within the ordinary skill in the art. The examiner has provided no evidence to refute this. What is more, as will be discussed in more detail in Section VII.C.4, below, the present specification provides detailed guidance (in both broad description and working examples) on how to perform the claimed methods using a variety of starting cell lines, and how to determine whether or not the method was successfully carried out. If the disclosure "adequately guide[s] the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility," the enablement requirement is met. *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). Furthermore, "[w]here the specification provides guidance in selecting the operating parameters that would yield the claimed result, it is fair to conclude that the

experimentation required to make a particular embodiment is not 'undue'." *PPG Indust., Inc. v. Guardian Indust. Inc.*, 75 F.3d 1558, 1565, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996).

The Examiner has mischaracterized the invention as calling for the "production" of "bacteria," and has applied the incorrect standard for enablement, requiring that the specification enable a method that uses "any and all" virally infected eukaryotic cells to produce "any and all bacteria," while the specification, combined with the ordinary skill in the art, in fact provides enablement of a number of modes of carrying out the claimed methods and obtaining the claimed cells. For these reasons, also, this rejection is improper and should be reversed.

4. The claims are enabled throughout their scope

a. The evidence of record proves enablement

The Examiner contends that the evidence of record does not establish "within a reasonable degree of scientific certainty that the claimed methods are enabled," as (according to the Examiner) it does not "demonstrate execution of the claimed methods [sic] steps would lead to the production of a bacteria containing a eukaryotic and/or viral gene." The Examiner's position is untenable, first because the claims recite neither "producing" nor "bacteria," but rather recite methods comprising a final step of "identifying ... a cell that is identifiable as a bacteria, and contains a eukaryotic and/or viral gene," and second, the evidence of record (which includes working examples, in addition to the results of an independent verification of the claimed methods) shows to within a reasonable degree of scientific certainty that the methods as presently claimed in fact *do* provide cells that are identifiable as bacteria, and contain a eukaryotic and/or viral gene.

Example 1 (pages 18-19) reports an experiment in which a line of a human capillary endothelial cells transformed with the murine L cell virus (RT-HCMV) was cultured under sterile conditions, with alternating anaerobic and aerobic culture phases as recited in the claims. Sterile conditions were maintained throughout the procedure. Control cultures of the same cells were cultivated under aerobic conditions only, but otherwise treated in the same manner as the experimental cultures. At the end of the

process, cells identifiable as *Micrococcus luteus* were isolated from the experimental culture.

Comparative Example D (pages 23-26) repeats the experiment of Example 1, using a different culture medium during the anaerobic/aerobic cultivation phases (medium 199 supplemented with 100 µg heparin/ml, 2 mM L-glutamine, and 10% heat-inactivated fetal bovine serum). Rigorous measures were taken to maintain sterility throughout the procedure, confirmed by testing methods that meet or exceed USP XXIII and/or 21 C.F.R. § 610 requirements. As with Example 1, the experimental cultures provided cells identifiable as bacteria, while the controls showed no observable microbiological growth. This example demonstrates that the claimed methods function equally well on different culture media.

In Example 4 (page 27), the results of Example 1 were replicated using three different virally-infected eukaryotic cells lines: retrovirally-transformed porcine cerebral microvascular endothelial cells (Robinson et al., *Blood* (1991) 77:294), L929 cells (ATCC CCL 1) transformed with murine retrovirus, and murine lymphoma cells (ATCC TIB52) transformed with Abelson MuLV retrovirus. In each case, cells identifiable as bacteria were observed in the cultures at the end of the process. No such cells were isolated from cultures of untransformed L929 and murine lymphoma cells. This example demonstrates that the claimed methods provide the same result using a variety of virally-infected eukaryotic cell lines as the starting material.

In Comparative Example 4/A (page 28), Example 1 was repeated using an SV40-transformed human colon cell line (ATCC CRL 1807) and an untransformed human colon cell line (ATCC HTB 38; HT-29 cells). At the end of the process, two gram-positive cocci and one gram-negative bacillus were isolated from the SV-40-transformed cell line culture, while no bacteria were isolated from the untransformed cell line culture. This example demonstrates that the presence of an infectious virus is integral to the process.

Example 5 (pages 28-34) reports the results of morphological and genomic analysis of nine isolates obtained by the claimed methods. Though extremely pleiomorphic, these isolates exhibited a variety of bacteria-like morphologies, such coccoid shape, gliding motility, "fried egg" morphology, and bacilloid shape. Pages 28-

29. They also were shown to contain retroviral DNA, such as the retroviral gag gene, and expression of the *gag* p30 protein was detected. Pages 29-31. The expression of several eukaryotic genes was also detected in the isolates, including protein kinase C, platelet-derived growth factor dimers AB, and human serum albumin, and the human eukaryote-derived Alu and LINES inter-repeat elements were detected in genomic DNA samples. Pages 31-34. These experiments demonstrate that the cells identifiable as bacteria that are provided by the claimed methods, using a number of different starting cell lines, not only exhibit bacteria-like morphology, but also contain eukaryotic and/or viral genes.

Several control experiments are also reported in the specification, which preclude to a reasonable scientific certainty that the cells identified after execution of the claimed methods are not either the result of microbiological contamination of the starting cell cultures, nor contaminants introduced during the procedure. In Comparative Example 1/A (page 19), controls containing medium only were treated as in Example 1, except that culture was carried out under aerobic conditions only. No microbial growth was observed in these cultures, demonstrating that there was no microbiological contamination in the culture media, nor contamination introduced during manipulation of the culture flasks in the experiments.

In Comparative Example 1/B (pages 20-21), the starting cell line used in Example 1 (RT-HMCV) was cultivated directly on bacteriological medium under conditions favoring the growth of bacteria and mycoplasmas, and no microbiological growth was detectable, even after growing the culture for several days under these conditions. This control experiment demonstrates that no overt microbial contamination was present in the actively-propogating RT-HCMV cells used in Example 1, even under conditions favoring the growth of bacteria.

In Comparative Example 1/C (pages 21-22), the RT-HCMV cell line was subjected directly to rigorous sterility and mycoplasma testing, using methods that meet or exceed USP XXIII and/or 21 C.F.R. § 58 requirements, and was found to be negative for the presence of bacterial, fungal and mycoplasmal contamination. This control experiment demonstrates that there was no detectable microbial contamination of the starting culture of Example 1 (RT-HCMV).

In Comparative Example 1/D (pages 22-23), RT-HCMV cells were cultured aerobically and subjected to non-oxygen stresses (various concentrations of sodium chloride, dimethylsulfoxide or hydrogen sulfide), at culture temperatures between 30 °C and 37 °C. No cells identifiable as bacteria were observed under any of these stresses, even after a week of cultivation under these conditions. These control experiments demonstrate that it was not stress, *per se*, which provides cells identifiable as bacteria after cultivation of RT-HCMV cells according to the claimed methods.

In Comparative Example 2/A (page 26), two cultures of RT-HCMV cells were grown for approximately 72 hours under anaerobic conditions only, but otherwise treated in the same manner as the experimental cultures of Example 1. Tandem controls of cells under aerobic conditions only and media-only (aerobic and anaerobic) were performed. No microbiological cultures were isolated from either the experimental or control cultures, demonstrating that it was not merely cultivation under anaerobic conditions that provides cells identifiable as bacteria after cultivation of RT-HMCV cells in accordance with the claimed methods.

This abundant experimental evidence provided in the specification demonstrates to a reasonable degree of scientific certainty that the claims are enabled well beyond the very narrow embodiment suggested by the Examiner, and indeed are enabled throughout their scope. *C.f.*, *Engel Indust.*, 946 F.2d at 1533, 20 USPQ2d at 1304.

Further evidence supporting enablement of the present claims is provided in the Final Report – "Evaluation of a Process for Generating Bacteria De Novo from Eukaryotic Cells," attached to the Robinson Declaration, and in the Steuer Declaration, which were submitted during prosecution of the parent to the present application, and thus form a part of the record in this case.[4] The Final Report contains the results of an independent verification of the claimed methods, performed by Microbiological Associates, Inc., of Rockville, Maryland, under the supervision of Dr. Anton Steuer. The study Conclusions appearing on the first page read as follows:

> Two runs involving the periodic reintroduction of an aerobic atmosphere during an anaerobic eukaryotic cell culture

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[4] The Robinson Declaration, the Final Report, and the Steuer Declaration were also re-submitted in the present case as attachments to the Applicant's last Amendment, dated February 10, 2006.

> phase resulted in the isolation of bacteria, specifically *Bacillus licheniformis*. Four different colony morphologies were observed. Two runs in which an aerobic atmosphere was not periodically reintroduced during an aerobic eukaryotic cell culture phase resulted in the isolation of no bacteria. All eukaryotic cell controls and media controls were negative. The isolation of bacteria from eukaryotic cells subjected to alternating anaerobic/aerobic cell culture conditions provides supporting evidence for the hypothesis of *de novo* evolution of bacteria from eukaryotic cells. On the other hand, the possibility of environmental contamination as a source of the bacterial isolates cannot be absolutely eliminated. Environmental contamination is unlikely due to the cGMP compliance procedures and practices employed in the performance of the sterility assays, which includes a stringent environmental and personnel monitoring program. Also, no tube, plate, or bottle inoculated with eukaryotic cell control samples or media control samples showed any microbial outgrowth. These negative results for all the numerous control samples tested minimized significantly the possibility of environmental contamination.

The four runs referred to in the Final Report Conclusion (two sets of two runs) were (1) RT-HCMV cells cultured on eukaryotic cell culture medium under anaerobic conditions only, followed by a phase of aerobic cultivation on bacterial culture medium, (2) RT-HCMV cells cultured on eukaryotic cell culture medium under anaerobic conditions, interrupted by a brief aerobic cultivation period, followed by a phase of aerobic cultivation on bacterial culture medium, (3) RT-HCMV cells cultured on eukaryotic cell culture medium under anaerobic conditions, interrupted by a brief aerobic cultivation period, followed by a phase of aerobic cultivation on bacterial culture medium, and (4) RT-HCMV cells cultured on eukaryotic cell culture medium under anaerobic conditions only, followed by aerobic cultivation on bacterial cell culture medium. *See*, Final Report, pages 3-6. Thus, runs 2 and 3 were performed in accordance with the claimed methods, and runs 1 and 4 were control runs performed under anaerobic conditions only.

The results of these four runs are reported at pages 8-9 of the Final Report. The two runs performed in accordance with the claimed methods, with anaerobic culture conditions interrupted by a brief period of aerobic culture (runs 2 and 3), each provided cells that were identified as bacteria, four colonies from run 2, and one colony from run 3. The two control runs performed under anaerobic conditions only (runs 1 and 4)

resulted in no observable microbial growth. Sterility tests performed before, during, and after each run were all negative for microbial outgrowth. These independent experiments can be reasonably interpreted as providing objective verification that the claimed methods provide the claimed results in a replicable manner.[5]

In his declaration, Dr. Steuer provided additional information and explanation about the experiments described in the Final Report. Dr. Steuer was responding to contentions by the Examiner made in the parent case that the findings in the Final Report were likely the result of microbiological contamination of the starting cell cultures, a contention that the Examiner has repeated in the final rejection here under appeal. *See*, Office Action, page 10 ("contamination is usually the first 'explanation' to be ruled out when confronted with data that flies in the face of accepted scientific theory"); page 11-12 ("In addition, it is unclear what precautions were taken in the instant case to assure that the bacteria harvested are not incidental contaminants inadvertently introduced into the cell culture"). Dr. Steuer directly addressed this issue in his Declaration:

> 5. I have read portions of an Office Action issued by the Patent and Trademark Office. The portions I read comments upon the attached Final Report, which I understand was previously submitted with a Declaration by Dr. Robinson. In paragraph no. 16, the Office Action states that the Final Report did not "rule out the possibility of bacterial contamination at each and every step of the claimed method." The Office Action therefore expresses the view that the results were due to contamination. I disagree with both that conclusion and the reasoning behind it that is presented in the Office Action.
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> 7. The Final Report provides extensive details regarding the specific sterility testing and aseptic cell culturing

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[5] It has been noted by the Examiner (Office Action, page 11), and by the Board (Remand, page 9), that the cells identified in the Final Report as bacteria were not screened in order to ascertain whether they contained a eukaryotic and/or viral gene. In view of the fact that the specification itself provides abundant proof that the cells produced by the claimed methods, identifiable as bacteria, do in fact, contain eukaryotic and/or viral genes, it is submitted that the experimental verification that the claimed methods produce cells identifiable as bacteria that is provided by the Final Report is sufficient to support the reasonable conclusion that the results reported in the specification in general are reproducible. Applicant wishes to stress that the Final Report is *confirmation* that the claimed methods are enabled/reproducible – the primary evidence of enablement is found in the specification disclosure itself.

> techniques that were employed. Additional verification of the quality of this work is provided on page 33 of the Final Report. ...
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> * * *
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> 8. It is my professional opinion that any scientific inquiry wherein one must "rule out" contamination, as set forth in the Office Action, is meaningless. Scientists in this field do not "rule out" contamination. This is why the Final Report states that "the possibility of environmental contamination as the source of the bacterial isolates cannot be absolutely eliminated." For this same reason I worded my conclusion that contamination "was highly unlikely." No scientist skilled in the field would state that the possibility of contamination had been "absolutely eliminated" or "ruled out" in any scientific procedure such as this. Rather, procedures are carried out under rigorously-controlled aseptic environments that minimize the possibility of contamination. The equipment, materials and procedures used at my company to test starting materials for contamination, and that were used in connection with Dr. Robinson's work, are recognized as meeting the highest quality standards. Thus, I concluded that the Patent Examiner has applied a requirement for "proving" a lack of contamination that is not applied by persons skilled in this field.

The Steuer Declaration, therefore, confirms that contamination was indeed "ruled out," to a reasonable degree of scientific certainty, as a source of the cells identified at the end of the experiments detailed in the Final Report. The law does not require more. *C.f.*, *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965) (applicant does not have to establish utility "beyond a reasonable doubt"); *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 884 (CCPA 1980) (no need to establish utility to a statistical certainty). Nor are these comments applicable merely to the specific experiments performed under Dr. Steuer's supervision, as he unambiguously states that the methods "used in connection with Dr. Robinson's work" also met the accepted scientific standards he describes.

The Examiner has ignored all of this unimpeached evidence in the record, or simply dismissed it as lacking sufficient credibility. Unless the Examiner provides substantial evidence in the record (as the Board has directed him to do, *see* Remand, pages 9-10), or sound reasoning establishing why a person of ordinary skill in the art would doubt its credibility, this evidence *must* be accepted as accurate, truthful, and probative. *In re Brana*, 51 F.2d at 1566, 34 USPQ2d at 1441; *see also, Fiers v. Revel*,

984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993)[6]; *C.f.*, MPEP, § 2107.01 (Rev. 5), page 2100-21.[7] As will be detailed below, the Examiner has failed to present any evidence to rebut or impeach the evidence of record, nor has he provided a persuasive, well-reasoned argument that calls into doubt the objective truth of the evidence of record. For this reason, also, this rejection is improper and should be reversed.

b. The Examiner has provided no rebuttal evidence in support of his arguments

The Examiner provides no more evidence to support his arguments in the final Office Action from which this appeal is taken than he had in his previous rejections, or in the previous appeal of this case, despite the clear direction of the Board that he do so. Remand, pages 9-10. The only evidence cited by the Examiner is an excerpt from a standard reference on cell culture (Freshney, 1984), for the unremarkable proposition that bacteria are common cell culture contaminants.

The specification describes in detail how to perform the claimed method in terms which correspond to the claims, and in fact provides a great deal of detail on how to adjust specific parameters in the process as needed, and furthermore demonstrates with working examples that the process functions as claimed. In contrast, the Examiner has done no more than assert in a conclusory manner that the claims are not enabled, and has provided no evidence or reasoning sufficient to call into question the presumptive enablement of the disclosure. The Federal Circuit has in fact found it to be reversible error for a lower court to find a lack of enablement where there was "no evidence that one skilled in the field of this invention could not make and use a product satisfying all the limitations of the claims, by following the inventors' disclosure and the knowledge of

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[6] "... a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraphs of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (emphasis original).

[7] "Similarly, Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered."

the art." *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1575, 18 USPQ2d 1001, 1007 (Fed. Cir. 1991).

The specification provides experimental data confirming that the claimed methods are enabled, data that the Examiner has not called into question. The Final Report and the Steuer Declaration provide independent verification of the results reported in the examples of the specification. The examiner has provided not one piece of evidence that rebuts or impeaches the credibility of the Final Report and Dr. Steuer's Declaration. The Examiner asserts that the Final Report lacks persuasive value, because contamination was not ruled out as a source of the cells provided by the claimed methods. The only "evidence" cited by the Examiner (the Freshney reference) does *not* establish that cell cultures that are found to be free of any microbial contamination under the accepted scientific standards in the field are still considered by workers in the field to be contaminated, nor does it establish that microbial contamination is a universal or inevitable phenomenon is the field of cell culture. As explained above in Section VII.C.4.a, the evidence of record establishes that this is not the case. The Patent Office cannot simply discount an applicant's statements supporting enablement by requiring "greater scientific precision than did any of the scientists whose testimony [is] presented." *Scripps*, 927 F.2d at 1575, 18 USPQ2d at 1007. In the present case, the evidence of record establishes that it is possible for one skilled in the art to successfully practice the claimed invention. There is no evidence in the record to the contrary, much less the substantial evidence that is required.

The Examiner also inserts into his rejection the unfounded assertion that "none of the Declarations of record were made by disinterested third parties," evidently for impeachment of the Final Report and supporting declarations. Office Action, page 10. While one of the declarations of record was made by the inventor, Dr. Douglas Robinson, for the purpose of introducing the Final Report into the record, the second Declaration, that of Dr. Steuer, is from a completely disinterested party – Dr. Steuer and his laboratory are in no way connected with the Applicant, other than as an independent contracting laboratory performing the verification experiments. If the Examiner is suggesting that Dr. Steuer was somehow "bought and paid for," which would be an offensive accusation against a respected scientist, to say the least, it is incumbent upon him to provide some shred of evidence to support this accusation. He has not done so.

The evidence of record stands unchallenged, and it shows that the claimed methods are in fact enabled by the specification disclosure. For this reason, also, this rejection should be reversed.

c. No undue experimentation is required to practice the claimed invention

The Examiner asserts that it would require undue experimentation to practice the invention throughout the scope of the claims. Office Action, pages 12-13. The Examiner poses a series of challenges in the form of questions or contentions, in lieu of providing actual evidence or reasoning in support of his contention. However, none of the questions posed by the Examiner suggest that the present claims are not enabled, nor are they sufficient to call into question the evidence of record supporting enablement.

The Examiner states that the specification "indicates that the cultured cells under anaerobic conditions results in the death of the eukaryotic cells" (though no citation is provided), making it "unclear if the eukaryotic cells are to be living or dead at this point [in the claimed process]." Office Action, page 12. The Examiner also asks which step of the process "leads to the production of the bacterium," and "[w]here are the genetic elements necessary for this event to occur (i.e., what is the origin of the bacteria)." *Id.* None of these questions is relevant to the issue of enablement, as they are directed to whatever underlying mechanism or principle is at work in the claimed methods.

It is not necessary to know or understand the answers to these questions in order to be able to practice the claimed method, and thus for there to be enablement. As stated in Section VII.B, above, in the discussion of the rejection under § 101, it is not a requirement of patentability that the manner in which the invention works be known or understood. *Fromson*, 720 F.2d at 1570, 219 USPQ at 1140; *Newman v. Quigg*, 877 F.2d at 1581, 11 USPQ2d at 1345; *accord*, *Cortright*, 165 F.3d at 1359, 49 USPQ2d at 1469. The claimed methods consist of a series of defined process steps, by which a starting culture of virally-infected eukaryotic cells is cultured, and whereby a defined type of cell ("a cell that is identifiable as a bacteria, and contains a eukaryotic and/or viral gene") is provided. Each of these process steps is defined in the specification, through both broad description and working examples. The Examiner has not explained why not having the answers to the rhetorical questions he poses would preclude a person having ordinary skill in the art from practicing the claimed methods.

Surprisingly, the Examiner states that "it is unclear what precautions were taken in the instant case to assure that the bacteria harvested are not incidental contaminants inadvertently introduced into the cell culture" (Office Action, pages 11-12), when the claims *expressly* recite that the starting culture be "free of any overt microbiological contamination," and that sterile conditions be maintained throughout the process. *See*, steps (a) – (e) of claim 30.

Equally surprising, the Examiner also asks, "how long is one of skill in the art to culture the virally infected eukaryotic cells," and also "how long does one of skill in the art have to culture the cells aerobically in order to 'produce' a bacterium containing a eukaryotic and/or viral gene?" Office Action, page 13. The claims themselves *expressly recite* the answers he seeks with regard to the anaerobic culture phase: "for a period of time between about 18 and 24 hours." *See*, Claim 30, steps (b) and (d); *see also*, specification at page 11, lines 8-11, and Examples. The specification describes the aerobic culture phase (recited in step (c) of claim 30) as "brief" (page 9, lines 15-18), Example 1 states that the culture is "briefly" exposed to aerobic conditions in the time it takes to aspirate a 2-3 ml sample from the culture flask (page 19, lines 4-7), and Comparative Example D expressly states that exposure to aerobic conditions (per step (c) of claim 30) was for less than 10 minutes during microscopic observations of the cell culture, and for another 2-3 minutes during a subsequent aerobic culture phase (page 24, lines 11-20). Also surprising is the Examiner's asking "which eukaryotic cells should one use, and what virus should be employed?" Office Action, page 13. The specification contains two pages of disclosure describing the cells and viruses that can be used in the claimed methods, not to mention the specific cell lines and viruses discussed in the Examples. *See*, pages 9-11; Examples 1 and 4.

The Examiner even asserts that "it is unclear how one skilled in the art would determine that the cell culture has these [eukaryotic and/or viral] 'genes' without undue experimentation (Office Action, page 13), when genetic screening and sequencing is (and was as of the September 25, 1996 priority date) a routine laboratory operation, in fact performed today by automated sequencers and computers. In any event, the specification in fact provides a great deal of guidance as to how to screen cell genomes and identify particular genes, enabling the determination of the genetic characteristics of the cells obtained by the claimed methods. *See*, *e.g.*, specification, page 15, lines 3-17; page 30, line 1 to page 33, line 22.

It is long settled by the courts that an applicant simply is not required to disclose every species within the scope of the claims, even in an "unpredictable" art. *See, e.g., Vaeck*, 947 F.2d at 496, 20 USPQ2d at 1445; *see also In re Angstadt & Griffin*, 190 U.S.P.Q. 214, 218 (CCPA 1976); MPEP, § 2164.02 ("Because only an enabling disclosure is required, applicant need not describe all actual embodiments."). Nor is an applicant required to test all the embodiments of the invention. *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (citing *Angstadt*). The question thus is whether or not the specification provides sufficient guidance to the person of ordinary skill in the art to practice the invention throughout its scope without resort to "undue experimentation." Under the proper standard, even a considerable amount of experimentation is not "undue" in the context of § 112, first paragraph, if that experimentation is routine, and in particular when one skilled in the art would know how to determine, using established methods, which embodiments are operative and which are not. *Atlas Powder*, 750 F.2d at 1576, 224 USPQ at 414. Even a considerable amount of experimentation is permissible, if it is routine to the person of ordinary skill in the art. *See, e.g., Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1360, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998) (lack of certainty in a process, requiring repetition, not attributable to a failure of disclosure in the patent in suit); *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) ("The key is undue,' not 'experimentation.'"). The Federal Circuit has noted that

> The Patent and Trademark Office Board of Appeals summarized the point well when it stated:
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> > The test is not merely quantitative, since a *considerable amount* of experimentation is permissible, if it is merely routine, or if the specification in question provides a *reasonable amount of guidance* with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

PPG Indust., 75 F.3d at 1564, 37 USPQ2d at 1623 (citing *Ex. Parte Jackson*, 217 U.S.P.Q. 804, 807 (BPA 1982)) (emphasis added).

For example, in *Wands* the Federal Circuit found that a claim covering a general class of monoclonal antibody-based assay methods did not lack enablement, because a person using the state of the art and the specification disclosure, could produce and screen new hybridomas to determine if they secreted antibodies falling within the

claimed class, without undue experimentation. 858 F.2d at 736-37, 8 USPQ2d at 1404 ("enablement is not precluded by the necessity form some experimentation such as routine screening [to identify hybridomas that secrete the desired antibody] ..."); *see also*, *Ajinomoto*, *supra*. The specification "need only teach those aspects of the invention that one skilled in the art could not figure out without undue experimentation." *Warner-Lambert Co. v. Teva Pharms. USA*, 418 F.3d 1326, 1377, 75 USPQ2d 1865, 1872 (Fed. Cir. 2005).

This is the case here, as all that is required in order to practice the invention are routine laboratory skills, such as the ability to locate (or create) virally-infected eukaryotic cells, culture them according to the claimed steps, and screen the resulting cell culture for cells indentifiable as bacteria that contain a eukaryotic and/or viral gene, all exercises that are well within the ordinary skill in the art. *See*, references cited throughout the specification. Even manipulation of process parameters such as culture medium, temperature, duration, etc., are all routine in the art. More to the point, the Examiner has provided no evidence to support the opposite contention, which is his burden. *In re Brana*, 51 F.3d at 1566, 34 USPQ2d at 1441.

The Examiner is simply incorrect in his assertion that the specification does not provide sufficient guidance to permit a person having ordinary skill in the art to practice the claimed invention. There are over nine pages in the specification devoted to precise directions for how to perform the claimed methods which, in addition to the working examples, permit a person having ordinary skill in the art to practice the invention as claimed. The selection of suitable virally-infected eukaryotic cells free of overt microbiological contamination, for use in the claimed methods (*e.g.*, claim 30, step (a)), is described in the specification at page 9, line 26 to page 10, line 26, as well as selection of suitable eukaryotic cell line and viruses, and methods, to create virally-infected eukaryotic cells. Comparative Example 1/D describes the creation of the RT-HCMV cell line in particular. Methods for carrying out the anaerobic culture phase of claim 30 steps (b) and (d) and the aerobic culture phase of step (c), including culture media, atmospheric conditions, temperature, and culture times, are disclosed in the specification at page 10, line 27 to page 12, line 5, as well as in the examples (*e.g.*, Example 1, Comparative Example D). Methods for carrying out the bacteriological culture phase of claim 30 step (e), including media, atmosphere, and temperature, are disclosed in the specification at page 12, line 7 to page 13, line 30, as well as in

Example 1 and Comparative Example D. Teachings relating to identification and characterization of the cells as recited in claim 30 step (f) are provided in the specification in, *e.g.*, Example 5, and in the numerous references cited in the Description of the Background Art (pages 1-5).

The specification provides more than sufficient guidance to enable a person having ordinary skill in the art to practice the claimed invention without undue experimentation. The Examiner has provided no evidence, or sound reasoning, that calls into question the objective truth, and presumptive accuracy, of the foregoing enabling description, or that establishes that it would require undue experimentation to apply those teachings (in combination with the knowledge of a person having ordinary skill in the art) to practice the claimed invention. For this reason, also, this rejection is improper and should be reversed.

5. The Examiner improperly focuses his enablement argument on the underlying mechanism of the claimed methods

The Examiner also, at least in part, appears to be requiring that the Applicant explain exactly what is occurring at each step of the process. For example, he asserts that it is unclear "how the cell culture is chosen to have a reasonable degree of certainty that bacteria as required can be 'produced', in the absence of positive steps to modify existing bacteria," whether "the eukaryotic cells are to be living or dead at this point [under aerobic conditions]," "what step actually produces the bacterium," and "where are the genetic elements necessary for this event to occur." Office Action, page 12. All of these "uncertainties" relate to the mechanism of the claimed methods, something that the Federal Circuit has expressly held is *not* relevant to the question of patentability. *Fromson*, 720 F.2d at 1570, 219 USPQ at 1140; *Newman v. Quigg*, 877 F.2d at 1581, 11 USPQ2d at 1345; *Cortright*, 165 F.3d at 1359, 49 USPQ2d at 1469.

The present claims do not recite the underlying cellular and/or molecular processes that occur during the practice of the claimed methods, nor does the practice of the claimed methods require knowledge or understanding of the underlying mechanisms and/or processes at work. The Examiner's focus on the possible mechanism(s) by which the claimed method operates, including uncertainties as to what exactly is occurring at a cellular or molecular level at particular process steps, is

therefore improper as a basis for a finding of a lack of enablement. For this reason, also, this rejection is improper and should be reversed.

6. Claims of substantially the same scope have been allowed in Europe

Although not a decision binding on the United States Patent and Trademark Office, there is probative evidence of enablement (as well as utility) for the present claims in the finding by the European Patent Office (EPO) that claims of substantially the same scope as those presently on appeal are patentable. The EPO found the following independent claim to be patentable (and thus industrially applicable or useful, enabled by the specification):

> 1. A method for isolating a bacterium that contains a eukaryotic and/or viral gene, comprising:
>
> (a) preparing a culture of virally-infected eukaryotic cells that is free of any overt microbial contamination, in an aseptic, eukaryotic cell culture medium,
>
> (b) subjecting the culture of step (a) to an anaerobic culturing phase under aseptic conditions wherein the culture is subjected to anaerobic culturing conditions corresponding to an atmosphere of 0-2 v/v % oxygen, for a period of time between about 18 and 24 hours, followed by
>
> (c) exposing the culture under aseptic conditions to oxygen conditions corresponding to an atmosphere containing greater than 2 v/v % oxygen,
>
> (d) subjecting the culture to an additional anaerobic culturing phase under aseptic conditions wherein the culture is subjected to anaerobic culturing conditions corresponding to an atmosphere of 0-2 v/v % oxygen, for a period of time of between about 18 and 24 hours, and
>
> (e) subjecting the culture of step (d) to an aerobic culturing phase under aseptic culturing conditions and corresponding to an atmosphere containing greater than about 2 v/v % oxygen in an aseptic bacterial culturing medium, and

(f) isolating from the culture of (e) a bacterium that contains a eukaryotic and/or viral gene.

The standard for enablement under European patent law is set out in Article 83 of the European Patent Convention (EPC):

> Article 83 - Disclosure of the Invention: The European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

While not identical in wording to the enablement provision of the first paragraph of § 112, the EPO standard is virtually the same as that in the United States. The guidelines for examining applications under Article 83 are set out in the "Guidelines for Examination, Part C, Chapter 4, "Patentability:"

> 4.11 - Insufficient disclosure
>
> Occasionally applications are filed in which there is a fundamental insufficiency in the invention in the sense that it cannot be carried out by a person skilled in the art; there is then a failure to satisfy the requirements of Art. 83 which is essentially irreparable. Two instances deserve special mention. The first is where the successful performance of the invention is dependent on chance. That is to say, the skilled person, in following the instructions for carrying out the invention, finds either that the alleged results of the invention are unrepeatable or that success in obtaining these results is achieved in a totally unreliable way. An example where this may arise is a microbiological process involving mutations. Such a case should be distinguished from one where repeated success is assured even though accompanied by a proportion of failures, as can arise e.g. in the manufacture of small magnetic cores or electronic components. In this latter case, provided the satisfactory parts can be readily sorted by a non-destructive testing procedure, no objection arises under Art. 83. The second instance is where successful performance of the invention is inherently impossible because it would be contrary to well-established physical laws - this applies e.g. to a perpetual motion machine. If the claims for such a machine are directed to its function, and not merely to its structure, an objection arises not only under Art. 83 but also under Art. 52(1) in that the invention is not "susceptible of industrial application" (*see* IV, 4.1).

The EPO examination guidelines can be found on-line at http://www.european-patent-office.org/legal/gui_lines/e/index.htm, the above-quoted section appearing at http://www.european-patent-office.org/legal/gui_lines/e/c_iv_4_1.htm. As can be seen from the foregoing, the substantive standard for enablement in Europe is essentially identical to that under U.S. law. The EPO's independent, though non-binding, finding of enablement for claims of substantially the same scope as the claims presently under appeal, is further probative evidence of enablement.

D. The Rejections Under 35 USC § 112, First Paragraph, Lack of Written Description, Lack Merit and Should Be Reversed

The Examiner has presented a new rejection of claims 4-14, 19-23 and 30-31 under 35 USC § 112, first paragraph, for lack of written description. Office Action, page 14. The Examiner asserts that the following phrases used in the claims "do not appear in the specification, or original claims as filed," and therefore constitute new matter:

- "free of any over [sic, overt] microbiological contamination" (claims 30 and 31);

- "under sterile culturing conditions" (claims 30 and 31);

- "one gene evolved from the genome of said eukaryotic cell" (claim 31);

- "identifiable as a bacteria and contains a eukaryotic and/or viral gene" (claim 30).

Office Action, pages 14-15.

In each case, the Examiner is applying an improper "*in haec verba*" test, requiring that these phrases appear exactly in the specification. This standard has been rejected repeatedly by the Federal Circuit. *See, e.g., Univ. of Rochester v. G.D. Searle*, 358 F.3d 916, 923, 69 USPQ2d 1886, 1892 (Fed. Cir. 2004) (not an *in haec verba* test – the specification must describe the claimed invention so that one skilled in the art can recognize what is claimed); *Cordis v. Medtronic*, 339 F.3d 1352, 1364, 67 USPQ2d 1876, 1885 (Fed. Cir. 2003); *Vas Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) ("the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*") (emphasis original); *All Dental Prodx*, 309 F.3d 774, 779, 64 USPQ2d 1945, 1948 (Fed. Cir. 2002) ("In order to comply with the written description

requirement, the specification 'need not describe the claimed subject matter in exactly the same terms as used in the claims; it must simply indicate to persons skilled in the art that as of the [filing] date the applicant had invented what is now claimed.'"); *Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1376, 62 USPQ2d 1917, 1922 (Fed. Cir. 2002) ("In order to satisfy the written description requirement, the disclosure originally filed does not have to provide in haec verba support for the claimed subject matter at issue.").

So long as a person having ordinary skill in the art would reasonably conclude that the specification describes the subject matter recited in the claims, the written description requirement of § 112, first paragraph, is satisfied. *Crown Operations*, 289 F.3d at 1376, 62 USPQ2d at 1922 ("Put another way, one skilled in the art, reading the original disclosure, must reasonably discern the limitation at issue in the claims."); *All Dental*, 309 F.3d at 779, 64 USPQ2d at 1948 ("However, the failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented.").

In each instance cited by the Examiner in this rejection, while the exact words noted are not stated in the specification, a person of ordinary skill in the art would reasonably conclude that the subject matter of the claims is described therein, and that the inventor had possession of the invention claimed, as of the filing date to which the present application claims priority.

1. "Free of any overt microbiological contamination"

The phrase "free of any overt microbiological contamination" is supported in the specification, *inter alia*, at pages 20 to 26. More specifically, the specification states (all emphasis added)

- "In order to determine whether or not **'overt' microbial contamination** exists in the RT-HCMV endothelial cell line, RT-HCMV endothelial cells are cultured directly into a variety of bacteriological media. ... After incubation for eight days in air at 37 °C, **no bacterial growth is observed** on any of these plates." Comparative Example 1/B, page 20, lines 2-6 and 18-19.

- "These experiments indicate that **the bacterial isolates are not contaminants in actively propagation RT-HCMV endothelial cells**

cultures. The experiments **rule out the possibility that contamination** of RT-HCMV endothelial cells occurred coincidentally ..." Comparative Example 1/B, page 21, lines 20-24.

- "**The RT-HCMV endothelial line is subjected to rigorous sterility and mycoplasma testing** in order to exclude the possibility that the cell line harbors bacterial, fungal or mycoplasma contaminants." Comparative Examples 1/C, page 21, lines 28-31.

- "The RT-HCMV endothelial cell line is found to be **negative for the presence of bacterial, fungal or mycoplasma contaminants**." Comparative Example 1/C, page 22, lines 8-10.

- "**No bacteria or mycoplasms are isolated from the bacteriological cultures** of experimental and control samples." Comparative Example 2/A, page 26, lines 27-29.

Each of these portions of the specification were cited in the Applicant's last amendment as providing support for new claims 30 and 31, wherein the phrase "free of any overt microbiological contamination" occurs. February 10, 2006 Amendment, page 6.

Although the exact phrase "free of any overt microbiological contamination" is not used in the specification, each of these statements, most particularly the first cited statement that experiments were carried out to determine whether there was "overt" microbial contamination in the starting cell line, which experiments showing that no overt microbial contamination was found, amply demonstrates that the specification describes methods wherein the starting eukaryotic cell line is "free of any overt microbiological contamination," in terms that would be readily understood by a person having ordinary skill in the art as describing such. The specification contains substantial disclosure showing that methods wherein the starting material is "free of any overt microbiological contamination" were in the possession of the inventor as of the priority date of the present application. The Examiner has not made any showing to the contrary, beyond the mere assertion of the lack of written description. This rejection is therefore unfounded, and should be reversed.

2. "Under sterile culturing conditions"

In addition to the portions of the specification noted above, which were all cited to the examiner in the Applicant's last Amendment, and which all reasonably convey to a person having ordinary skill in the art that the processes recited in claims present claims

are carried out under sterile culture conditions, support for this claim term is also found in the following statements in the specification (all emphasis added):

- "Each of the steps preferably is carried out under **aseptic conditions,** thereby eliminating or reducing the possibility of contamination." Page 9, lines 21-23.

- "The gas line into the anaerobic jar is connected to a 0.20 µm **sterile** filter in order to filter out possible microbial contaminants. The anaerobic jar, containing **sterilely vented** culture flasks with eukaryotic cells, is sealed and periodically flushed with **sterile** nitrogen gas for 2-3 hours." Example 1, page 18, lines 17-23.

- "The jar is opened to the atmosphere and the **sterilely vented** culture flasks are quickly sealed to prevent exposure to aerobic conditions." Example 1, page 18, line 31 – page 19, line 2.

- "After 1-2 hours, medium samples of 2-3 ml are aspirated from each flask **under sterile conditions** for further microscopic examination ..." Example 1, page 19, lines 4-7.

- "The **sterilely vented** culture flasks are place in the anaerobic jar, which is flushed with **sterile** nitrogen gas as described previously." Example 1, page 19, lines 8-11.

- "... the RT-HCMV endothelial cell suspensions are filtered through **sterile**, 0.22 µm Millipore filters ..." Example 1, page 19, lines 16-18.

- "Medium is aspirated from six of the flasks, and each of these flasks is re-fed with **sterile** nitrogen (N_2)-flushed medium ..." Comparative Example D, page 23, lines 16-18.

- "All medium is filtered using a Corning 0.22 µm **sterile** filter unit. Prior to feeding, the medium is flushed with **sterile** nitrogen gas for 10-15 minutes." Comparative Example D, page 23, lines 21-24.

- "... the chamber is sealed and purged with **sterile-filtered** N_2 four times over approximately a two hour period ..." Comparative Example D, page 23, lines 27-29.

- "The flasks are then transferred to the experimental anaerobic chamber, which is sealed and flushed with **sterile** N_2 ..." Comparative Example D, page 24, lines 21-23.

In addition to these express references to sterile conditions being maintained and tested during the process, references to procedures known on the art to assure sterility, *e.g.*, filtration through a 0.22 µm Millipore filter, further demonstrate possession of a method wherein culture steps are carried out under sterile conditions. The specification,

therefore "reasonably apprises" the person having ordinary skill in the art that methods performed "under sterile culturing conditions" were in the possession of the inventor as of the priority date of the application. The Examiner has not made any showing to the contrary, beyond the mere assertion of the lack of written description. This rejection is therefore unfounded, and should be reversed.

3. "One gene evolved from the genome of said eukaryotic cell"

The specification specifically states that "the 'eukaryotic gene' present in the bacterium need not be identical to the gene present in the eukaryotic cell." Page 7, lines 12-14. The specification goes on to describe how the gene contained in the cells obtained by the claimed method can differ from the gene present in the eukaryotic cell. Page 7, lines 15-25. A change in a gene over time, for example over the period required by the claimed methods, can properly be termed "evolution" of that gene. *Webster's New World College Dictionary*, 4th Ed., defines "evolve," in the biological context, as "to develop gradually by a process of growth and change." The relevant portion of *Webster's Dictionary* are in the record as an attachment to the February 10, 2006 Amendment. Of course, "gradual" is a relative term in the case of bacteria, which can go through a number of generations in even a few hours. Thus, the period of time elapsed in the practice of the claimed invention (up to several days), gradual, and even dramatic, changes in a gene can occur. This is seen for example in the frequent, and sometimes rapid, development of antibiotic resistance in bacteria under the environmental pressure of exposure to an antibiotic. "Evolution," or being "evolved" is the clearest way to describe this process as it occurs in the methods recited in the present claims, and as it is described in the passage of the specification quoted above.

The specification, therefore, fairly apprises the person of ordinary skill in the art that the inventor had possession of cells which, *inter alia*, contain a "gene evolved from the genome of" the starting eukaryotic cell line from which it was derived. This rejection is therefore unfounded, and should be reversed.

4. "Identifiable as a bacteria and contains a eukaryotic and/or viral gene"

The phrase "identifiable as a bacteria and contains a eukaryotic and/or viral gene" is supported throughout the specification, as indeed this is an important aspect of the invention. This phrase is properly broken down into two parts, "identifiable as a

bacteria" and "contains a eukaryotic and/or viral gene." Support for the claim limitation that the cells obtained by the claimed method are "identifiable as bacteria" is found, *inter alia*, in the following statements in the specification (all emphasis added):

- "In some physical or morphological aspects the bacteria obtained according to the present invention **can resemble bacteria** reported to have been isolated from cancer patients and AIDS patients, that is, the so-called pleomorphic or cell-wall deficient bacteria." Page 7, lines 26-30.

- "Additionally, bacteria obtained according to the present invention have been isolated **and typed** as *Bacillus licheniformis*, a GRAS (generally-recognized-as-safe) microorganism." Page 9, lines 1-4.

- "After several days, distinct colonies appear on the plates. **For the isolation of *Micrococcus luteus***, a 0.8 µm sterile filter is used to exclude eukaryotes prior to aerobic bacteriological culturing." Page 19, lines 24-26.

- "After one to several weeks of incubation, **five Gram-positive rods** are isolated from the bacteriological cultures of experimental eukaryotic cell samples subjected to anaerobic eukaryotic cell culture conditions with periodic introductions of an aerobic atmosphere during the eukaryotic cell culture phase." Page 26, lines 5-10.

- "All isolates are ***typed as Bacillis licheniformis***." Page 26, lines 12-13.

- "One of these colonies **is classified as a *Staphlococcus hemolyticus***." Page 27, lines 11-13.

- "**Gram-positive bacteria** are isolated from the cultures originally containing retrovirally transformed porcine cerebral microvascular endothelial cells." Page 27, lines 22-25.

- "In the murine lymphoma cells transformed with the Abelson MuLV, **gram-positive baccili** are obtained." Page 27, lines 29-30.

- "Two **gram-positive cocci and one gram-negative bacillus** are isolated from SV40 cells during the bacteriological culturing phase." Page 28, lines 9-11.

Furthermore, the entirety of Example 5.A, entitled "Characterization of the Bacteria, Morphology" is devoted to discussion of the identification of the cells produced by the claimed method as various bacterial types. Page 28, line 14 to page 29, line 22. For instance, Example 5.A states that

> "[f]ive of these bacterial isolates were subjected to **extensive bacteriological analyses by the ATCC**.

> Individual isolates **were classified** as *Micrococcus luteus* (isolate 1; Group III), *Staphylococcus aureus* (isolate 2P; Group II), *Staphylococcus epidermidis* (isolate 5; Group I), *Staphylococcus hemolyticus* (isolate 1c; Group II)."

Page 28, lines 25-31. Example 5.A also includes the statement that

> "[a]nother five bacteria derived with the subject process **were classified** as different isolates of *Bacillus licheniformis*, a GRAS microorganism."

Page 29, lines 4-6.

Each of these statements in the specification relate to the identification of bacterial cells, *e.g.*, via typing by Gram-staining, or classification as particular bacterial species. This reasonably conveys to a person having ordinary skill in the art that the inventor was in possession of the claimed invention, and specifically that the claimed method results in the production of cells that are "identifiable as bacteria."

The specification also provides a written description of cells identifiable as bacteria that "contain[ ] a eukaryotic and/or viral gene" in, *inter alia*, the following statements (all emphasis added):

- "One object of the present invention is to provide **novel bacteria containing and expressing eukaryotic genes**." Page 5, lines 25-26.
- "A further aspect of the present invention is to provide a process for producing biological products, in particular human biological products, by culturing **such bacteria** under conditions **wherein such products are expressed by the bacteria** and are recoverable from the bacterial culture medium." Page 6, lines 3-8.
- "These and other objects, which will become apparent during the following detailed description, have been achieved or are achievable as a result of the inventor's discovery that it is possible to culture virus-infected eukaryotic cells under low oxygen conditions so as to produce **bacteria which contain and preferably express animal and/or viral genes**." Page 6, lines 24-30.
- "The **bacteria** of the invention typically are highly pleomorphic, **can contain both eukaryotic and viral genes** and preferably **express at least one eukaryotic gene** such that the gene product is recoverable upon culturing the cells." Page 7, lines 4-8.
- "The **'eukaryotic gene' present in the bacterium** beed nbot be identical to the gene present in the eukaryotic cell." Page 7, lines 12-14.

Example 5.B, entitled "Presence of Retroviral DNA," describes in detail the detection of expressed viral genes in the cells produced by the claimed methods. Page 29, line 23 to page 31, line 13. Example 5.C, entitled "Presence of animal DNA, animal genes, and animal gene products or proteins," describes in detail the detection of expressed eukaryotic genes in cells produced by the claimed methods. Page 31, line 14 to page 34, line 19.

The foregoing portions of the specification reasonably and clearly convey to a person having ordinary skill in the art that the inventor was in possession of the claimed methods, specifically of methods that result in the isolation of cells "identifiable as bacteria and contain[ing] a eukaryotic and/or viral gene." The Examiner has not made any showing to the contrary, beyond the mere assertion of the lack of written description. This rejection is therefore unwarranted, and should be reversed.

E. The Rejections Under 35 USC § 112, Second Paragraph, Lack Merit and Should Be Withdrawn

The Examiner has presented a new rejection of the claims under § 112, second paragraph, as failing to set forth the subject matter which the applicant regards as his invention. Office Action, page 15. The Examiner asserts that statements made by the Applicant's attorney during earlier prosecution of the present case establish that claims 4-14, 19-23 and 30-31 do not correspond in scope to the invention. In particular, the Examiner refers to a November 17, 2003, Reply, which he quotes as stating that "the instant claims are drawn to 'methods for **producing a bacterium** that contains a eukaryotic and/or viral gene which comprises culturing virally-infected eukaryotic cells under low-oxygen conditions.'" Office Action, page 15. The Examiner asserts that

> this statement indicates that the invention is different from what is defined in the claims(s) because said statement requires that the genome of the 'produced' bacteria is prokaryotic in nature suggesting that the claimed method induces a 'de-evolution' of the eukaryotic cell.

Office Action, pages 15-16. The Examiner states that "[t]he present claims are drawn to cells identifiable as a bacteria and containing a eukaryotic and/or viral gene," but then states that "[s]aid claims are drawn to any cell that has the phenotype of a prokaryote regardless of its genomic organization (i.e., eukaryotic vs. prokaryotic genome) not a bacteria and containing a eukaryotic and/or viral gene." Office Action, page 16.

This rejection is confusing to the point of incomprehensibility, and for that reason alone should be reversed. On the one hand, the Examiner is saying that the Applicant had represented during prior prosecution that the *claims* are drawn to methods for producing bacteria containing a eukaryotic and/or viral gene, which is different from what is defined in the present claims because it requires that the "produced" bacteria have a prokaryotic genome. On the other hand, the Examiner is saying that the present claims *are* drawn to methods for producing cells identifiable as bacteria and containing a eukaryotic and/or viral gene (a statement with which the Applicant agrees), but that they are also drawn to "any cell that has the phenotype of a prokaryote regardless of its genomic organization," which is different from how the Applicant had previously described as the *invention*. However, nowhere does the Examiner fully or clearly explain how any of this establishes that the *present* claims do not correspond in scope to what the Applicant considers to be his *invention*.

The best that the Applicant can make of this argument is that the Examiner has taken the Applicant to have represented in a prior communication with the Patent Office that the *invention* is a method for producing actual bacteria (*i.e.*, a prokaryote having a prokaryotic genome) that contains a eukaryotic and/or viral gene, while the present *claims* are drawn to methods for producing cells that are *identifiable* as bacteria, but do not necessarily have a prokaryotic genome. If the Applicant is correct in his interpretation of these statements, then there is no basis therein for rejecting the claims under § 112, second paragraph. First, on its face the prior statement by the Applicant describes the then-pending *claims*, not what he considered to be the invention in a broader sense. Second, neither the quoted statement regarding the then-pending claims, nor the then-pending claims themselves, nor the present claims, differ in scope from what the Applicant considers to be comprised by his invention. *See*, Section V, "Summary of the Claimed Subject Matter," above.

Nonetheless, the Examiner concludes that what the Applicant considers to be his *invention* is different from what is presently *claimed*. The Applicant has consistently stated (albeit in various ways in an attempt to make very clear what was meant) that his invention comprises a method whereby virally-infected eukaryotic cells are taken and cultured under alternating anaerobic and aerobic conditions, which results in the production of cells that appear in many respects to be prokaryotes (bacteria), but contain a eukaryotic and/or viral gene. As pending at the time of the Applicant's statement

quoted above, the claims *did* recite "production" of a "bacterium," both terms to which the Examiner objected at the time. The Applicant explained repeatedly that the terms "production" and "bacteria" were used in the claims as the best ones available to describe the claimed process and the cells obtained thereby, but never represented that the invention related to literal creation of bacteria – *i.e.*, cells having essentially a prokaryotic genome with one or more eukaryotic and/or viral genes. On Remand, the Board suggested certain language to describe the cells of the present claims in terms that are not as loaded with meaning, to wit, "cells identifiable as bacteria, that contain a eukaryotic and/or viral gene" (*see* Remand, page 8), which was adapted by the Applicant and now appears in the claims on appeal. The prior statement by the Applicant quoted by the Examiner is not *proof* that the present claims are not drawn to what he considers to be the invention, but is rather simply a reflection of the fact that the claim language *has changed* since that statement was made. Thus, there is no lack of correspondence between the scope of the present claims and what the Applicant considers to be his invention. For this reason, also, this rejection should be withdrawn.

The Examiner has also rejected claims 4-14, 19-23 and 30-31 as being indefinite. Claims 30 and 31 are asserted to be rendered indefinite by the use of the term "under sterile conditions." According to the Examiner, "[i]t is unclear how one can culture cells 'under sterile conditions" when, by definition, 'sterile conditions' require the lack of living matter." Office Action, page 16. The Examiner is using a definition of "sterile conditions" that is completely at odds with its normal and accepted usage in the biological arts. *C.f.*, Steuer Declaration, and the Final Report for further evidence of the art-accepted use of the terms "sterile" and "sterility" in the context of the cell culture arts. One "sterilizes" a wound in order to prevent infection, but that of course does not mean that *all* living matter in the wound is killed. Cell culture medium and equipment is "sterilized," to eliminate unwanted contamination, but is then used to grow desired cells. Furthermore, the specification goes into great detail regarding the "sterile conditions" used in the process (*see*, Section VII.D.2, above), which make it clear that the term as used in the claims carries its normal meaning of excluding unwanted microbial contamination. Because this rejection is based on an unreasonable definition of "sterile conditions" that is a odds with its ordinary and customary meaning in the art, and with its use in the specification, this rejection is improper and should be reversed.

Claim 31 has been rejected as vague and indefinite by the use of the phrase "gene evolved from the genome of said eukaryotic cell." Office Action, page 16. According to the Examiner, the meaning of this term is unclear because it is not explicitly defined in the specification. However, "[a] claim is definite if 'one skilled in the art would understand the bounds of the claims when read in light of the specification.'" *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 424 F.3d 1374, 1383, 76 USPQ2d 1741, 1746 (Fed. Cir. 2005) (quoting *Personalized Media Comm's, LLC v. ITC*, 161 F.3d 696, 705, 48 USPQ2d 1880 (Fed. Cir. 1998)); *Amgen*, 927 F.2d 1t 1217, 18 USPQ at 1030 ("A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed."). In the present case, the term "gene evolved from the genome of said eukaryotic cell" would be readily understood by a person having ordinary skill in the art in the context of the present invention, as explained in detail in Section VII.D.3, above. This meets the standard for definiteness, as recently re-articulated by the Federal Circuit:

> "We have stated the standard for assessing whether a patent claim is sufficiently definite to satisfy the statutory requirement as follows: If one skilled in the art would understand the bounds of the claim when read in light of the specification, then the claim satisfies section 112 paragraph 2."

Exxon Research and Eng'g Co. v. U.S., 265 F.3d 1371, 1375, 60 USPQ2d 1272, 1276 (Fed. Cir. 2001). Read in the context of the specification, the term "gene evolved from the genome of said eukaryotic cell" has a readily identifiable meaning, and a person having ordinary skill in the art would readily understand the meets and bounds of the claims as they relate to that term. Thus, this term, as used in claim 31, is neither vague nor indefinite, but rather describes that aspect of the invention as precisely as the subject matter permits, in terms grounded in the specification disclosure that would be easily understood by a person having ordinary skill in the art. "[I]f the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and the scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." *Shatterproof Glass Corp. v. Libbey-Owens Ford. Co.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985).

Because the term "gene evolved from the genome of said eukaryotic cell" is as precise as the subject matter permits, and furthermore would be readily understood by a person having ordinary skill in the art, this rejection is improper and should be reversed.

Conclusion

In view of the above, it is abundantly clear that the Examiner erred in finally rejecting claims 4-14, 19-23 and 30-31. It is therefore respectfully requested that the Board reverse the Examiner's rejections of claims 4-14, 19-23 and 30-31.

The Office is authorized to charge any fees related to this communication to Deposit Account No. 11-0600.

Respectfully submitted,

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CLAIMS APPENDIX

4. The method according to claim 30, wherein said anaerobic culture conditions comprise an atmosphere containing less than or equal to 1 v/v% oxygen, based on the total volume of atmosphere.

5. The method according to claim 4, wherein said atmosphere contains less than 0.1 v/v% oxygen, based on the total volume of atmosphere.

6. The method according to claim 30, wherein said eukaryotic cells are retrovirally-infected mammalian cells.

7. The method according to claim 6, wherein said mammalian cells are human cells.

8. The method according to claim 30, wherein said eukaryotic cells are mammalian, avian or fish cells.

9. The method according to claim 8, wherein said eukaryotic cells are endothelial cells.

10. The method according to claim 30, wherein said eukaryotic cells are mammalian brain capillary endothelial cells.

11. The method according to claim 30, wherein said eukaryotic cells are infected with a virus selected from the group consisting of the murine L-cell virus, simian immunodeficiency virus (SIV), human immunodeficiency virus (HIV), Ableson murine leukemia virus and Maloney murine leukemia virus.

12. The method according to claim 11, wherein said virus is the murine L-cell virus.

13. The method according to claim 30, wherein said culturing step is carried out at a temperature between about 20° and about 50°C.

14. The method according to claim 30, wherein said culturing step is carried out at a temperature of about 37°C.

19. The method according to claim 30, wherein said eukaryotic cells are human brain capillary endothelial cells infected with the murine L-cell virus.

20. The method according to claim 30, further comprising filtering the cells cultured in step (d) prior to said aerobic culturing step (e).

21. The method according to claim 20, comprising filtering the cells through a 0.1 to 0.8 μm filter.

22. The method according to claim 21, wherein said filter is 0.1 to 0.45 μm.

23. The method according to claim 22, wherein said filter is 0.22 μm.

30. A method comprising:

(a) preparing a culture of virally-infected eukaryotic cells that is free of any overt microbiological contamination, in a sterile eukaryotic cell culture medium,

(b) subjecting the culture of step (a) to an anaerobic culturing phase under sterile conditions wherein the culture is subjected to anaerobic culturing conditions corresponding to an atmosphere of 0-2 v/v % oxygen, for a period of time between about 18 and 24 hours, followed by

(c) exposing the culture of step (b) under sterile conditions to oxygen conditions corresponding to an atmosphere containing greater than 2 v/v % oxygen, followed by

(d) subjecting the culture of step (c) to a second anaerobic culturing phase under sterile conditions wherein the culture is subjected to anaerobic culturing conditions corresponding to an atmosphere of 0-2 v/v % oxygen, for a period of time of between about 18 and 24 hours, followed by

(e) subjecting the culture of step (d) to a second aerobic culturing phase under sterile culturing conditions and corresponding to an atmosphere containing greater than about 2 v/v % oxygen in a sterile bacterial cell culture medium, and

(f) identifying in the culture of step (e) a cell that is identifiable as a bacteria, and contains a eukaryotic and/or viral gene.

31. A pleiomorphic cell, characterized by

(a) being a non-transgenic cell;

(b) being derived from a eukaryotic cell by a process comprising the steps of

(i) preparing a culture of virally-infected eukaryotic cells that is free of any overt microbiological contamination, in a sterile, eukaryotic cell culture medium,

(ii) subjecting the culture of step (i) to an anaerobic culturing phase under sterile conditions wherein the culture is subjected to anaerobic culturing conditions corresponding to an atmosphere of 0-2 v/v % oxygen, for a period of time between about 18 and 24 hours, followed by

(iii) exposing the culture of step (ii) under sterile conditions to oxygen conditions corresponding to an atmosphere containing greater than 2 v/v % oxygen, followed by

(iv) subjecting the culture of step (iii) to a second anaerobic culturing phase under sterile conditions wherein the culture is subjected to anaerobic culturing conditions corresponding to an atmosphere of 0-2 v/v % oxygen, for a period of time of between about 18 and 24 hours, followed by

(v) subjecting the culture of step (iv) to a second culturing phase under sterile culturing conditions and corresponding to an atmosphere containing greater than about 2 v/v % oxygen in a sterile bacterial cell culture medium;

(c) containing at least one gene evolved from the genome of said eukaryotic cell.

EVIDENCE APPENDIX

No evidence has been submitted.

RELATED PROCEEDINGS APPENDIX

There are no related proceedings.